REMARKS

Claims 32-35 and 69-70 are currently pending. Applicants thank the Examiner for the review of the instant application, and for withdrawing the rejection of Claims 32-35 under the judicially created doctrine of obviousness-type double patenting. Applicants appreciate the indication that the Examiner believes Claim 70 is in condition for allowance. The rejections of the remainder of the presently pending claims are respectfully traversed.

Rejection Under 35 U.S.C. §103(a)

The Examiner has maintained the rejection of Claims 32-35, and has rejected Claim 69 as allegedly being upatentably obvious over McCarty et al (US Patent No. 5,707, 970; "McCarty") in view of Speck (US Patent No. 6,006,659; "Speck"), Harrison's Principles of Internal Medicine ("Harrison's") and Levere (US Patent No. 5,217, 997; "Levere"). Regarding Claim 69, the Examiner argues that McCarty teaches that arginine is a precursor for nitric oxide, and that nitric oxide exerts vasodilatory effects. The Examiner then concludes that since arginine is present in the arginine silicate complex, it would have been obvious that the arginine silicate complex would provide an increase in vascular relaxation. Regarding Claims 32-35, the Examiner maintains the following: (1) McCarty teaches that arginine teaches administration of arginine silicate inositol for the treatment of atherosclerosis or as a supply of arginine; (2) Speck teaches that atherosclerosis is a disease of the coronary vascular system, and thus treatment of atherosclerosis with arginine silicate inositol would treat diseases secondary to atherosclerosis; (3) Speck teaches atherosclerosis can lead to reduced perfusion into the extremities or brain infarct, which the Examiner alleges involves microvascular/macrovascular complications, thus treatment of atherosclerosis with arginine silicate inositol would treat diseases secondary to coronary vascular disease; (4) Harrison's teaches that a major goal of therapy for nephrosclerosis is control of hypertension, Levere teaches arginine for the treatment of hypertension, and McCarty teaches arginine silicate inositol for the supply of arginine, and thus it would be obvious to treat nephrosclerosis with arginine silicate inositol.

Applicants respectfully disagree.

To establish a *prima facie* case of obviousness a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. Second, there must be

a reasonable expectation of success found in the prior art. Third, the prior art must reference must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991

The teachings of McCarty do Not Render Claims 32-35 Obvious in view of Speck

a. McCarty and Speck Do Not Teach or Suggest Arginine Silicate Inositol for Treating Disease Secondary to Coronary Vascular Disease

Applicants submit that the teachings of McCarty and Speck cannot support a prima facie case of obviousness for Claims 32-35. The Examiner argues that because McCarty teaches administration of arginine silicate inositol for the treatment of atherosclerosis, and Speck teaches that "atherosclerosis *can* lead to reduced perfusion into the extremities or brain infarct" (Office Action, Oct. 8, 2004, p. 4), that the skilled artisan would appreciate that administration of arginine silicate inositol per the teachings of McCarty would "could. . . [prevent those diseases secondary to atherosclerosis] from occurring or else effectively ameliorate[] [them]." *Id.* Applicants submit, and the Examiner has acknowledged, that McCarty does not teach arginine silicate inositol for "*treating* a disease *secondary to* coronary vascular disease." *Id. at 3.* (Emphasis added) In essence, the Examiner asserts that the usefulness of a compound (i.e., arginine silicate inositol) for the treatment of one type of primary coronary vascular disease (i.e., atherosclerosis) renders that compound useful for the treatment of a variety of conditions, merely because a subset of those conditions may arise as a consequence of atherosclerosis. While the treatment of atherosclerosis may *prevent the emergence* of some types of diseases secondary to atherosclerosis, Applicants submit that nothing in McCarty and Speck suggests the same treatment (administration of arginine inositol silicate) used for treating atherosclerosis, as described in McCarty, would "effectively ameliorate" diseases secondary to atherosclerosis, or coronary vascular disease in general. Further, the Examiner has provided no support for the conclusion that arginine silicate inositol could "effectively ameliorate" any of the above conditions. In short, at most, McCarty and Speck teach a treatment that may prevent the worsening of conditions that may arise as secondary to atherosclerosis. Applicants submit that this is not the same as treating those diseases, and that nothing in McCarty and Speck teaches or suggests arginine silicate inositol is useful in *treating* diseases secondary to coronary vascular disease.

McCarty describes atherosclerosis as "a complex and chronic disease involving the gradual accumulation of lipids, collagen, elastic fibers and proteoglycans in the arterial wall."

Col. 1, lines 10-12. According to the Examiner, Speck discusses "reduced perfusion into the extremities" and "brain infarct," which are microvascular/macrovascular complications. (Office Action, Oct. 8, 2004, p. 4) Applicants submit that those skilled in the art would not find it obvious that a treatment directed to accumulation of lipids, collagen, elastic fibers and proteoglycans in the arterial walls would be useful for treating "reduced perfusion into the extremities," particularly where the reduced perfusion to the extremities is caused by something other than atherosclerosis, e.g., vasoconstriction. In instances where reduced perfusion to the extremities arises from something other than atherosclerosis, the treatment would not logically involve treatments aimed at curing atherosclerosis. Likewise, one skilled in the art would not necessarily find it obvious that a treatment directed to atherosclerosis would be useful for treating brain infarct.

Given the above, Applicants submit that McCarty and Speck fail to provide suggestion or motivation to treat diseases secondary to coronary vascular disease with arginine silicate inositol, and that these references do not render Claims 32-35 obvious.

b. McCarty and Speck Provide No Reasonable Expectation That Arginine Silicate Inositol Will Successfully Treat Disease Secondary to Coronary Vascular Disease

As discussed above, the PTO must show that the references relied upon for a rejection under 35 U.S.C. § 103(a) must lead one of ordinary skill in the art to believe that he or she would have a reasonable expectation of success in practicing the claimed invention in view of the cited art. See, In re Merck & Co., Inc., 231 U.S.P.Q. 375 (Fed. Cir. 1986); M.P.E.P. §2143.02. Applicants respectfully submit that there is no reasonable expectation of success in *treating* diseases secondary to coronary vascular disease, such as nephrosclerosis, abnormal liver lipid concentrations, microvascular complications, and macrovascular complications provided in McCarty and Speck. While McCarty and Speck may discuss treatment of atherosclerosis, the references are completely silent as to whether arginine silicate inositol would be efficacious in the *treatment* of diseases secondary to coronary vascular disease. Applicants agree that the treatment of atherosclerosis may be useful in *preventing* the onset or occurrence of diseases that arise as a result of atherosclerosis, but submit that this is not the same as treating those diseases themselves. Because the references provide no expectation of success in reversing or ameliorating diseases secondary to coronary vascular disease, they cannot form the basis of a rejection under 35 U.S.C. § 103(a).

The teachings of McCarty do Not Render Claims 32-35 Obvious in view of Harrison's and Levere

a. McCarty, Harrison's and Levere Do Not Teach or Suggest Arginine Silicate Inositol for Treating Disease Secondary to Coronary Vascular Disease

Applicants submit that the teachings of McCarty, Harrison's and Levere cannot support a *prima facie* case of obviousness for Claims 32-35. The Examiner argues that Claim 32 reads on nephrosclerosis, and that Harrison's teaches that a major goal in the treatment of nephrosclerosis is the control of hypertension. According to the Examiner, Levere and McCarty teach that arginine is useful in the control of hypertension, and that arginine silicate inositol is a good source of arginine. From the above, the Examiner arrives at the conclusion that it would have been obvious to one skilled in the art that arginine silicate inositol is useful in treating diseases secondary to coronary vascular disease. Nephrosclerosis is a disease characterized by hardening of the kidneys. Applicants submit that given the cited references, one skilled in the art would not find it obvious that a compound (i.e., arginine silicate inositol) useful for treating hypertension would be useful in *treating* nephrosclerosis, particularly in light of the fact that nephrosclerosis does not necessarily arise as a result of hypertension. See, e.g., Fervenza, F., "Nephrosclerosis," from <http://www.emedicine.com/med/topic1611.htm>, p. 2, last visited April 6, 2005, attached herewith as Exhibit 1. (Reporting that the term "the pathologic changes [associated with nephrosclerosis] are also observed in kidney biopsy specimens of patients who are normotensive, particularly those of advanced age or with diabetes."); Bos, W. et al., (2001) "Renal Vascular Changes in Renal Disease Independent of Hypertension," *Nephrol. Dial. Transplant*, 16: 537-541, attached herewith as Exhibit 2. It is clear from the above that one skilled in the art would not find it obvious that a compound useful in the control of hypertension will be useful in the treatment of nephrosclerosis, or any other disease. It is *not* evident from Harrison's, McCarty, and Levere, that administration of arginine silicate inositol would have any effect on reversing or *treating* nephrosclerosis, particularly in patients who have nephrosclerosis but are normotensive. As such, Applicants submit that the above references do not establish render Claims 32-35 obvious.

b. McCarty, Harrison's and Levere Provide No Reasonable Expectation That Arginine Silicate Inositol Will Successfully Treat Disease Secondary to Coronary Vascular Disease

McCarty, Harrison's and Levere would not lead one of ordinary skill in the art to believe that he or she would have a reasonable expectation of success in practicing the claimed invention in view of the cited art, as required to form the basis for a rejection under 35 U.S.C. § 103(a). McCarty discloses treatment of hypertension with arginine. However, based on the discussion above, one skilled in the art would not expect that a compound useful for treating hypertension would also be useful for treating or alleviating nephrosclerosis. Applicants submit that the treatment of atherosclerosis may be at most useful in *preventing* the onset or occurrence of diseases that arise as a result of atherosclerosis, including nephrosclerosis, but further submit that this is not the same as treating those diseases themselves. Because the references provide no expectation of success, they cannot form the basis of a rejection under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing arguments, Applicants respectfully submit that the present application is in condition for allowance. Nevertheless, the PTO is invited to contact the undersigned at the telephone number appearing below to discuss any remaining issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Apr. 6, 2005

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EXHIBIT 1

Nephrosclerosis

Last Updated: September 28, 2004

Synonyms and related keywords: HN, hypertension, hypertensive nephrosclerosis, hypertensive nephropathy, nephroangiosclerosis, end-stage renal disease, ESRD, end stage renal disease, end-stage kidney disease, end stage kidney disease, hypertensive retinopathy, left ventricular hypertrophy, minimal proteinuria, progressive renal insufficiency, benign nephrosclerosis, nephroangiosclerosis, blood pressure control, BP control

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Background: According to the 2003 US Renal Data System (USRDS), hypertensive nephrosclerosis (HN) accounts for at least 26 % of patients reaching end-stage renal disease (ESRD) each year in the United States. HN is the second most common cause of ESRD in white people (24%) and is the leading cause of ESRD in black people (33%).

The term HN has traditionally been used to describe a clinical syndrome characterized by long-term essential hypertension, hypertensive retinopathy, left ventricular hypertrophy, minimal proteinuria, and progressive renal insufficiency. Most cases are diagnosed based solely on clinical findings. In fact, most of the literature dedicated to HN is based on the assumption that progressive renal failure in a patient with long-standing hypertension, moderate proteinuria, and no evidence suggesting an alternative diagnosis characterizes HN. The lack of firm criteria on which to base a histologic diagnosis and the lack of a clear demonstration that hypertension initiates the development of renal failure likely indicate that the true prevalence of HN has been overestimated.

As reported by Zuccalà and Zucchelli (1996), part of the confusion in the classification of HN stems from the use of the word nephrosclerosis. Coined almost a century ago by Theodor Fahr, nephrosclerosis simply means hardening of the kidney. In the United States and Europe, the terms HN, benign nephrosclerosis, and nephroangiosclerosis are commonly used to describe the same clinical condition. These terms refer more to the pathologic changes attributed to the effects of hypertension than to the clinical picture of the disease in question. Unfortunately, the pathologic changes are not specific to hypertensive renal injury; they are also observed in kidney biopsy specimens of patients who are normotensive, particularly those of advanced age or with diabetes.

A couple of important points have been made in recent studies. First, among an unselected sample of community-based participants in the Framingham Heart Study, the combination of hypertension and a mild reduction in the glomerular filtration rate (GFR) was found to be an important risk factor for the development of new-onset kidney disease. Other factors noted were diabetes, obesity, smoking, and a low high-density lipoprotein cholesterol level. Second, systolic BP is a strong, independent predictor of a decline in kidney function among older persons with isolated systolic hypertension. This is a significant finding because most cases of uncontrolled hypertension in the United States are due to systolic hypertension among older adults.

Most patients reaching ESRD from any cause are hypertensive, with nephrosclerosis being the classic finding in end-stage kidneys. Regardless of the etiology, once hypertension develops, a cycle of renal injury, nephrosclerosis, worsening of hypertension, and further renal injury is established. As a result, in a patient presenting with ESRD, determining whether nephrosclerosis is the cause or the consequence of chronic renal injury may be difficult.

Pathophysiology: Two pathophysiologic mechanisms have been proposed for the development of HN. One mechanism suggests that glomerular ischemia causes HN. This occurs as a consequence of chronic hypertension resulting in narrowing of preglomerular arteries and arterioles, with a consequent reduction in glomerular blood flow. Alternatively, glomerulosclerosis occurs because of glomerular hypertension and glomerular hyperfiltration. According to this theory, hypertension causes some glomeruli to become sclerotic. As an attempt to compensate for the loss of renal function, the remaining nephrons undergo vasodilation of the preglomerular arterioles and experience an increase in renal blood flow and glomerular filtration. The result is glomerular hypertension, glomerular hyperfiltration, and progressive glomerular sclerosis. These mechanisms are not mutually exclusive, and they may operate simultaneously in the kidney.

Furthermore, Tracy and Ishii (2000) postulate that nephrosclerosis may not be a single disease entity in the sense of responding to a single etiology such as hypertension or aging. Rather, nephrosclerosis appears to be multifactorial. It may, in part, be a consequence of fibroplasias in microscopic arteries causing ischemic damage to some nephrons; however, it also may be the end product of a mixture of converging separate pathologic conditions, ie, "second hits," of which only some are known.

Genetically mediated animal models of hypertension, including the Dahl rat and the spontaneous hypertensive rat (SHR), have been used to investigate the role of hypertension in the development of nephrosclerosis. Fundamental differences exist among the strains and between rat and human hypertension. The SHR most closely resembles human essential hypertension. The SHR becomes hypertensive without exposure to salt. Micropuncture studies in hypertensive rats demonstrate an increased preglomerular vasoconstriction that is effective in preventing the development of intraglomerular hypertension. In fact, the SHR develops little renal damage, unless uninephrectomized. In these animals, rigorous BP control does not prevent the development of proteinuria and the pathologic changes of HN. The Dahl salt-sensitive rat develops proteinuria before hypertension and before a high-sodium diet is administered. Of note, no glomerular hypertension occurs.

In patients with essential hypertension, hemodynamic studies frequently show a reduction in renal blood flow. The increased preglomerular vasoconstriction of the afferent arteriole and interlobular artery is thought, at least initially, to exert a protective effect in the glomerulus. With time, sclerosis of the preglomerular vessels causes further reduction in renal blood flow. The GFR is maintained because of increased intraglomerular pressure secondary to efferent arteriolar vasoconstriction and systemic hypertension. Eventually, glomerular ischemia and tubular ischemia develop. Considered together, these data suggest that hypertension precedes and accelerates arteriolar changes in the renal vessels.

Genetics

A genetic link for hypertension and related renal failure is supported by studies demonstrating familial clustering of HN in black people and, to the same extent, in white people. The idea of a genetic predisposition to renal injury in black people is

also supported by reports of clinical trials.

In the Multiple Risk Factor Intervention Trial (MRFIT), no changes in the reciprocal creatinine slope were observed in white people, but a significant loss in kidney function was observed in black people despite similar levels of BP control. Similarly, secondary analyses from the Modification of Diet in Renal Diseases (MDRD) study demonstrated that at equivalent mean arterial pressures greater than 98 mm Hg, black patients had a reduction in their GFR at a rate of approximately 1 mL/min/y more than white patients. These observations have led to investigations into genetic factors predisposing to renal damage.

In different populations, the *DD* genotype is associated with a higher prevalence of progressive renal disease. This genotype is more common in the black population than the white population. Black people with hypertension also have increased angiotensinogen mutations compared with white people with hypertension. Homozygous D polymorphism is associated with an enhanced pressor response to angiotensin I. In patients with immunoglobulin A nephropathy, homozygous D polymorphism appears to influence the rate of progression of renal diseases and the response to ACE inhibitors; thus, ACE polymorphism could be an important modulator for the renal response to injury and the response to treatment in persons with HN. Whether these data are also applicable to the black population remains to be determined.

Frequency:

- **In the US:** Over the last 2 decades, ESRD attributed to HN has contributed significantly to the 7-11% per year increase in new patients starting dialysis in the United States. According to the 2003 USRDS, rates of ESRD caused by hypertension increased almost 50%, while the increase was 11% for glomerulonephritis and 21% for cystic kidney disease. When patients are separated according to race, hypertension is the leading cause of ESRD in black people, accounting for 34% of patients initiating dialysis during this period.

- **Internationally:** In Europe, according to the European Dialysis and Transplant Association registry, HN is a less common cause of ESRD, accounting for 12% of new patients starting renal replacement therapy. However, the reported prevalence varies among different countries, with France and Italy reporting HN as being responsible for ESRD in 21% and 27% of patients starting dialysis, respectively. In Asia, hypertension appears to be a relatively infrequent cause of ESRD, with both Japanese and Chinese registries reporting 6% and 7%, respectively. Establishing whether these differences are real or reflect differences in accuracy of diagnosis or criteria for diagnosis in different countries is difficult.

Mortality/Morbidity: According to the 2003 USRDS, the annual mortality rate for patients on hemodialysis in the United States is 23.3%. HN accounts for more than one third of patients on hemodialysis.

Race: Marked differences exist in the prevalence of HN among patients of different ethnic backgrounds. Although black people make up 12% of the US population, they account for 28% of the patients on renal replacement therapy. With perhaps the exception of atherosclerotic renal disease, black people are at an increased risk of renal diseases from any cause, especially HN. In black people, HN occurs earlier, is more severe, and more often causes ESRD (36.8% in black patients vs 26% in white patients).

- In persons of all age groups, ESRD is more common in black people. The increased susceptibility of black patients with hypertension to develop progressive renal failure cannot be explained solely by the higher prevalence of hypertension, severity of hypertension, or socioeconomic factors. The MRFIT indicated that effective BP control was associated with stable renal function in white people but not in black people. Socioeconomic differences alone among races do not explain the higher prevalence of HN in black people because stroke and cardiovascular mortality rates have decreased equally in both white and black populations.

- Several renal, hormonal, and physiologic differences, including increased BP sensitivity to a high-salt diet, increased renal vascular resistance, and decreased renal blood flow, are suggested as an explanation for the susceptibility of black people to HN. A decreased nephron number secondary to low birth weight, which is more common in black people, is also suggested to be a part of the increased risk for progressive renal failure in this patient population. In addition, renal angiograms of black patients with hypertension and normal renal function show increased tortuosity and occlusion in the interlobular and arcuate arteries compared with those of white patients with similar BPs and renal function.

Age: The diagnosis of HN increases with advancing age. The peak age for the development of ESRD in white patients is 65 years and older, while the peak age is 45-65 years in black people. In most cases, the diagnosis of HN in older patients is made clinically because of the reluctance to perform a renal biopsy in this elderly population. Even when a renal biopsy specimen is available, distinguishing vascular lesions due to aging from those due to hypertension may be difficult. In this respect, atheromatous renal vascular disease has been increasingly recognized as a common finding in patients older than 50 years.

- Rimmer and Gennari (1993) estimate that atheromatous renal vascular disease accounts for 5-15% of all patients who develop ESRD each year. In addition, cholesterol embolism resulting from atheromatous plaque disruption with subsequent shedding of cholesterol crystals into the renal circulation is frequently diagnosed in this patient population. Both renal artery stenosis and cholesterol embolism are associated with renal microvascular lesions and with glomerular sclerosis. Neither of these findings should be underestimated because patients older than 65 years represent at least 45% of the total population of patients on dialysis in the United States.

- Similarly, Appel et al (1995) found bilateral renal artery stenoses in 11% of

patients on hemodialysis who are older than 50 years. After extrapolating their results to the total number of cases of ESRD, multiplying by the number of patients aged 50 years or older, and multiplying by the number of patients with ischemic renal disease, Appel et al concluded that more than 3500 cases of ischemic renal disease remain undiagnosed each year in the United States. If these predictions are correct, ischemic renal disease is likely the fourth most common cause of ESRD in patients older than 50 years.

- More recently, Hansen et al (2002) provided the first population-based estimate of the prevalence of renovascular disease among free-living elderly American participants of the Cardiovascular Health Study (CHS). This is a multicenter, longitudinal cohort study of cardiovascular disease risk factors, morbidity, and mortality among free-living adults older than 65 years. CHS participants numbered 870, and each underwent renal duplex sonography to assess for the presence or absence of renovascular disease, defined as greater than or equal to 60% diameter-reducing renal artery stenosis or occlusion. The results of this study show that renovascular disease is present in 6.8% of all individuals, regardless of race (6.9% of white participants and 6.7% of black participants).

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History: Patients may present with hypertension, its complications (eg, heart failure, stroke), and/or symptoms of uremia. In most patients, hypertension is present for many years (usually >10 y), with evidence of periods of accelerated or poorly controlled BP. Features suggesting the diagnosis of HN are as follows:

- Black race
- Hypertensive retinal changes
- Left ventricular hypertrophy
- Long-standing or very severe hypertension
- Proteinuria less than 0.5 g/d
- Hypertension diagnosed prior to the onset of proteinuria
- Hypertension preceding renal dysfunction
- No evidence of another renal disease
- Biopsy findings compatible with the diagnosis

Physical: Upon physical examination, evidence of hypertension-related target

organ damage includes hypertensive changes in the retinal vessels and signs of left ventricular hypertrophy. Hemorrhages or exudates are characteristic of accelerated hypertension, and papilledema is a feature of malignant hypertension.

Causes: No causes for HN are known. See Pathophysiology. A gene that predisposes to hypertensive renal injury has been identified in rats. To date, however, no specific hypertensive ESRD-associated gene has been identified in humans. Correct identification of HN susceptibility genes requires accurate HN phenotyping. The major impediment to establishing a reliable HN phenotype is the absence of strong clinical criteria to distinguish HN from other renal diseases. Genetic approaches to HN require careful scrutiny of clinical diagnoses before assigning phenotypes to study subjects.

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Other Problems to be Considered:

Renal atherosclerotic disease
Cholesterol microembolization
Malignant hypertension
Mildly active primary renal disease

Hypertension and atherosclerotic renal artery disease

Hypertension is frequently associated with atheromatous renal artery disease (RAS), especially in elderly patients. Atherosclerotic RAS is present in 7% of the general population older than 65 years (regardless of race) and in 20-45% of patients older than 50 years who have had an angiography performed because of peripheral or coronary disease.

The predominant clinical manifestations of atherosclerotic RAS include hypertension, renal failure (ischemic nephropathy), recurrent episodes of congestive heart failure, and flash pulmonary edema. Sudden worsening of renal function in a patient who is hypertensive and who was started on an ACE inhibitor is also suggestive of renal vascular disease.

Not all patients with RAS are hypertensive. Olin et al (2002) studied 395 consecutive patients who had undergone arteriography as part of an evaluation for aortoiliac or peripheral vascular disease and who did not have the usual clues to suggest RAS and found greater than or equal to 50% stenosis in approximately 35% of nondiabetic patients and in up to approximately 50% of diabetic patients.

Goals for identifying RAS include improving BP control and preserving renal function. The diagnosis of RAS can be established with the use of Doppler ultrasound scanning, magnetic resonance angiography using gadolinium as the contrast agent, or renal arteriography. Most patients are treated medically, but

when progressive hypertension, renal insufficiency, or circulatory congestion develops, renal revascularization should be considered. Renal revascularization (ie, percutaneous transluminal angioplasty/stent, surgery) may result in improvement in BP control in 50-80% of patients, but cure is unusual in patients with long-standing hypertension. Vascular intervention (percutaneous transluminal angioplasty or surgery) may also improve or stabilize renal function in selected patients.

The complication rate for renal artery stenting varies considerably between centers, and complications include hematomas, retroperitoneal hemorrhage, arterial dissections, pseudoaneurysm formation, arteriovenous fistula, rupture of the renal artery, vessel occlusion, or infection. Restenosis occurs in 14-20% of cases. In addition, patients may develop contrast-induced acute renal failure and cholesterol embolism. As a result, approximately 20% of patients who undergo vascular intervention experience a worsening of renal function or develop ESRD; additionally, BP is not improved in 20-50% of patients.

To date, no randomized trial has shown a survival benefit for either endovascular or surgical revascularization compared with medical management. Recognizing RAS and identifying patients who will benefit from revascularization remains a significant challenge for clinicians. For a review on this subject, see the 2003 article by S.C. Textor.

Cholesterol microembolization

Besides renal artery stenosis, cholesterol microembolization can also mimic HN. Cholesterol embolization is frequently found at autopsy in white patients older than 50 years, at a rate varying from 4.7-17.7%. This condition is also observed in black patients; it was present in 2 of 39 patients in the African American Study of Kidney Disease and Hypertension (AASK). Making the diagnosis is not difficult when patients present acutely following an angiographic procedure, transluminal angioplasty, or anticoagulant treatment or as a complication of vascular surgery. However, in many cases, the disease is chronic, patients are relatively asymptomatic, and, presumably, the disease is the result of a spontaneous renal cholesterol embolism. These patients may present with nephrotic-range proteinuria. Renal biopsy specimens show classic needle-shaped crystals in the glomeruli or renal arteries.

Renal biopsy findings

Renal biopsy findings that mimic HN can be observed in various clinical conditions, even in the absence of hypertension. These conditions include hemolytic uremic syndrome, postpartum renal failure, scleroderma, chronic radiation nephritis, and obesity. Reaching an accurate diagnosis can be difficult in patients presenting late in the course of renal failure.

Lab Studies:

- Laboratory evaluation includes the following:
  - Baseline complete blood cell count
  - Creatinine level
  - Electrolyte status
  - Urinalysis
  - Either a spot urine test for albumin or creatinine ratio or a 24-hour urine collection - determine total protein excretion
- In a large series of patients, most had urine protein excretion of lower than 1 g/d; howeve patients with biopsy-proven HN, a 24-hour urinary protein excretion greater than 1 g/d w described. When secondary changes of focal segmental glomerulosclerosis (FSGS) rela hyperfiltration develop, proteinuria can increase to the nephrotic range.
- Innes et al (1993) reviewed 185 cases of patients with renal biopsy specimens that were solely as HN. In 40% of these patients, urinary protein excretion was greater than 1.5 g/c excreting more than 3 g/d and 18% having serum albumin values less than 3 g/dL. Simil were reported by Harvey et al (1992). Freedman et al (1994) questioned these findings b many biopsy specimens showed segmental and diffuse glomerulosclerosis. Harvey et al these lesions to the effect of hypertension, but Freedman et al felt that these patients ha FSGS, not HN.
- The contrasting conclusions of Harvey et al and Freedman et al highlight the problems o distinguishing HN from primary glomerular disease purely on clinical grounds. Neverthel black people who are hypertensive, do not have diabetes, and have mild-to-moderate re and proteinuria less than 2 g/d, renal biopsy specimens are likely to show morphological consistent with the clinical diagnosis of HN. On the other hand, the diagnosis of HN in a white patient is unusual, and these findings suggest an alternative diagnosis.

Imaging Studies:

- An echocardiogram may be required to assess left ventricular size.
- Renal imaging with either an ultrasound or an intravenous pyelogram reveals that kidney usually symmetric and may be normal or modestly reduced.
- The renal calices and pelves are normal.
- Renal asymmetry or irregularities in the contour raise the possibility that hypertension co secondary to renal artery stenosis or reflux nephropathy.

Other Tests:

- ECG typically shows left ventricular hypertrophy; however, this may not be evident on th tracings.

Procedures:

- A definitive diagnosis of HN cannot be made without a renal biopsy, especially in the whi population. In the absence of a renal biopsy, the diagnosis of HN is one of exclusion.

Histologic Findings: Upon gross pathologic examination, the kidneys are shrunken and scar According to Tracy and Ishii (2000), the descriptive pathologic abnormalities of benign nephro seen on renal biopsy specimens include glomeruli obsolescence, interstitial fibrosis, arterial int fibroplasia, arteriolar hyalinization in arterioles (most notably afferent), and small arteries (arcu interlobular artery, see Image 1).

Myointimal hypertrophy of the interlobular arteries, hyaline degeneration, and sclerosis of affer arterioles are the most characteristic findings of HN. Interlobular arteries often show reduplicat internal elastic lamina and medial hypertrophy. The arterial wall shows hyaline changes, appe eosinophilia, and distinctively periodic acid-Schiff–positive deposits (see Image 2). The arteriol narrowed.

Early in the disease process, the glomeruli are normal. With time, ischemic changes become v including wrinkling of the glomerular tuft and thickening of the Bowman capsule (see Image 3) Occasionally, mild focal mesangial cell proliferation and matrix expansion occur. Eventually, c glomerular hyalinosis and obsolescence ensue with the development of secondary tubular atr interstitial fibrosis (see Image 4). In contrast, the presence of enlarged glomeruli and the abse collapse of the basement membrane suggest that the patient is most likely developing second superimposed on primary hypertensive disease.

With immunofluorescence, no specific pattern is noted, with the exception of an increased pre immunoglobulin M deposits in the arterioles and mesangium. Fibrinoid necrosis and microinfar features of malignant or accelerated hypertension, not nephrosclerosis. Of note, electromicros examination of renal biopsy specimens may help to distinguish primary FSGS from secondary primary FSGS, foot process effacement is widespread; in secondary FSGS, it is more localize

As noted by Fogo et al (1997), none of the above lesions is pathognomonic. Consider the diag HN only when the constellation of these changes is present in the absence of other lesions of glomerular disease.

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Medical Care: BP control is closely linked to the decline in cardiovascular and cerebrovascula rates over the last 3 decades. Recent epidemiologic studies underscore that even modest dec renal function, usually identified by a serum creatinine level of greater than 1.4 mg/dL or estim of less than 60 mL/min, magnify long-term cardiovascular risk. One interpretation of these find nephrosclerosis is part of generalized vascular disease elsewhere. With regard to antihyperter therapy and ACE inhibitor administration, patients with cardiovascular disease and impaired re function benefit proportionately more than those with normal kidney function. The National Kid

Foundation has identified that a reduction in the cardiovascular risks associated with renal dis critical focus of the care of patients with renal disease.

Treatment of hypertension in patients with parenchymal renal disease is also effective in prese function, particularly in proteinuric renal diseases such as diabetic nephropathy. Similarly, posi evidence suggests that antihypertensive treatment protects renal function in patients with mali hypertension.

Remarkably, whether treating hypertension is effective to prevent ESRD attributed to HN is no This is surprising because the percent of patients aware of their hypertension has increased fr 84% over the last 20 years. At the same time, the percent of patients on medications increase to 73%. However, recent studies have shown that BP is adequately controlled (<140/90 mm H 25-30% of patients taking antihypertensive medication.

Early data from large treatment surveys provide little information on the ability of antihypertens treatment to prevent progressive renal deterioration in patients with essential hypertension. Fo Beevers and Lip (1996) analyzed the combined results of 9 major treatment trials of mild hype which included 21,826 patients. According to their analysis, the number of patients randomize treatment who subsequently developed renal failure was the same (ie, 50) as those patients w randomized to placebo treatment.

Similarly, among the 2125 cases of men with hypertension followed by Madhavan et al (1995) evidence showed that controlling BP influenced renal function. Patients with hypertension who treated for up to 5 years exhibited GFRs and renal plasma flow rates similar to those obtained who were not treated. In the Hypertension Detection and Follow-up Program (HDFP), renal fu found to decline in some patients despite optimal antihypertensive treatment.

Zucchelli and Zuccalà (1998) followed the cases of 30 patients with essential hypertension for 20 years. In 15 of these patients, renal function was maintained, while the other 15 patients sh onset of renal impairment. Both groups were matched for age, sex, and treatment duration. At the study, BP profiles indicated similar or better pressure control in patients with progressive r disease compared with patients with normal renal function.

Similarly, Rostand et al (1989) retrospectively reviewed the records of 181 patients with hyper patients with a primary renal disease diagnosed based on either suggestive medical history or biopsy findings, those with urinary protein excretion greater than or equal to 1.5 g/d or a serur level greater than or equal to 1.5 mg/dL were excluded from the analysis. Ninety-four patients considered as having essential hypertension. Fourteen patients (15%) had an increase in thei creatinine level greater than 0.4 mg/dL from baseline. However, renal function declined and w independent of the degree of BP control. In addition, Whelton and Klag (1989) reviewed 6 larg antihypertensive treatment trials and reported that the total number of renal events was small, statistical difference between the treated groups and the placebo groups.

Toto et al (1995) reported on a long-term, prospective, randomized trial of 87 patients with the diagnosis of HN to determine whether strict versus conventional BP control was associated wi decline in renal function. In this trial, strict control of BP (ie, mean diastolic BP of 81 mm Hg ± not better than conventional BP control (ie, mean diastolic BP of 86.7 mm Hg ± 1.1) for preser function; however, both groups experienced a slow decline in the GFR.

More recently, Hsu (2001) conducted a meta-analysis of 10 randomized controlled trials of antihypertensive drug therapy of more than 1 year's duration that reported renal dysfunction as outcome. Trials enrolling only those patients with known renal insufficiency or established rena parenchymal disease were excluded. Totals included 26,521 individuals, 114,000 person-year renal outcomes. This meta-analysis failed to demonstrate a difference between treated and un subjects regarding the development of ESRD. Notable limitations of this study were that the st not address how stricter or longer-term control of BP would affect the incidence of renal dysfur (2) was unable to evaluate the effects of newer classes of antihypertensive medications such a inhibitors or angiotensin receptor blockers (ARBs).

Similarly, Ruilope et al (2001) reported on the renal function effect of intensive lowering of BP hypertensive participants of the Hypertension Optimal Treatment (HOT) study. Baseline serum values were available in 18,597 patients. Among them, 470 subjects had a serum creatinine va than 1.5 mg/dL. Their conclusion was that in contrast to patients with normal renal function, the frequency of major cardiovascular events did not differ in the 3 groups of patients with mild ren insufficiency randomized to different diastolic BP targets. In most patients, no significant chang serum creatinine values were noted at the end of the 3- to 9-year treatment period. However, a group of patients (0.58% of the total study population) had deterioration of renal function (increa >30% over baseline and final serum creatinine values >2 mg/dL) despite a satisfactory reducti diastolic BP.

A criticism to the study is that systolic BP remained more than 10 mm Hg (mean) above the go than 130 mm Hg, which has been recommended for patients with high serum creatinine levels attained BP differed by only 4 mm Hg among the lowest and highest target groups (139.7-143 Whether tighter systolic BP control could have had an impact in this population with progressiv impairment cannot be addressed with the available data. In any case, the group of hypertensiv in whom renal function progressively deteriorated was small.

Studies of black patients with hypertension have not consistently shown a benefit of BP contro progression of renal disease. Determining whether more intense BP control may slow renal dis progression in black patients is the objective of the AASK trial, the results of which have recen published.

The study involved 1094 black people aged 18-70 years with GFRs from 20-65 mL/min/1.73 m other identified causes of renal insufficiency. Based on a 3 X 2 factorial design, participants we randomized equally to a usual mean arterial pressure goal of 102-107 mm Hg or to a lower go mm Hg or lower and to treatment with 1 of 3 antihypertensive drugs (ie, beta-blocker, ACE inh calcium channel blocker). The primary analysis was based on the rate of change in GFR (GFF Secondary outcome included confirmed reduction in GFR by 50% or by 25 mL/min/1.73 m^2 fro mean of the 2 baseline GFRs, ESRD, or death.

After randomization, BP decreased from 152/96 mm Hg to 128/78 mm Hg in the lower BP grou from 149/95 mm Hg to 141/85 mm Hg in the usual BP goal group. A mean separation of approx 10 mm Hg mean arterial pressure was maintained throughout most of the follow-up period. Ho mean GFR decline did not differ significantly between the lower and the usual BP groups durir follow-up period from baseline to 4 years. Similarly, the number of events (ie, rates/participant the main clinical composite outcome (ie, declining GFR events, ESRD, death) was no different the BP groups. As such, results of the AASK trial do not support additional BP reduction as a s prevent progression of HN.

These results are in agreement with previous findings in the MDRD study, which showed no e GFR decline in patients assigned to rigorous BP control (goal mean arterial pressure <92 mm participants <60 y or <98 mm Hg in participants >60 y) compared with the usual BP goal (ie, < Hg in participants <60 y or <113 mm Hg in participants >60 y). However, further analysis show protective effect of tight BP control in patients with proteinuria at baseline.

Finally, the Systolic Hypertension in the Elderly Program (SHEP) prospectively studied the rel between baseline BP and an incident decline in kidney function among 2182 participants olde years with serum creatinine values less than 2 mg/dL enrolled in the placebo arm of the study. in kidney function was defined as an increase in serum creatinine values of greater than or eq mg/dL. Over the 5 years of follow-up, 226 subjects experienced an increase in serum creatinin greater than or equal to 0.4 mg/dL. A decline in kidney function was associated with systolic B tended to be greater in persons with diabetes and in black persons. However, the report did n the relative contribution of patients in these 2 categories to the 226 persons with declining kidr function.

Taken together, in the universe of individuals with essential hypertension, a review of the evid shows that (1) in patients with HN, the absolute risk of developing renal insufficiency that will l ESRD is low (as opposed to hypertension being a promoter of existing renal disease, which is established fact) and (2) the progression of renal disease is not clearly related to hypertension because recent therapeutical trials have failed to demonstrate that intensive antihypertensive t slows the progression of renal diseases attributed to HN.

The following outlines the indications, effects, and adverse effects of the most commonly used antihypertensive medications.

Diuretics

- Effects and indications
    - Induce natriuresis
    - Thiazide-induced vasodilation occurs
    - Reduce target organ morbidity and mortality in hypertension
    - Maximal BP-lowering effects achieved at low doses (12.5-25 mg/d)
    - Potentiate antihypertensive effects of all other blood pressure medications
    - Antihypertensive effect observed in all demographic groups
    - Thiazides superior to loop diuretics as antihypertensive agents.
- Adverse effects
    - Hypokalemia (dose dependent)
    - Hyperlipidemia (usually short-lived)

- Glucose intolerance (dose dependent)
- Hyperuricemia and gout (dose dependent)
- Thiazides ineffective when GFR is less than 30 mL/min
- Impotence
- Hypochloremic metabolic alkalosis (dose dependent)

ACE inhibitors

- Effects and indications
  - Reduce proteinuria
  - Specific renal protective effect both in diabetic and nondiabetic renal impairment
  - Reduce morbidity and mortality rates in congestive heart failure
  - Monotherapy less effective in older patients (>50 y)
  - Larger doses required in black patients
  - Inhibit or blunt all adverse metabolic effects of thiazides
  - Dose reduction required in renal failure
  - Reduce left ventricular hypertrophy and thirst
- Adverse effects
  - Cough (approximately 10%)
  - Angioedema (rare)
  - Hyperkalemia (especially in renal tubular acidosis type IV)
  - GFR reduction in patients with impaired renal function
  - May precipitate acute renal failure in patients with renal artery stenosis
  - Interfere with breakdown of bradykinin
  - Contraindicated in pregnancy

Calcium channel blockers

- Effects and indications
  - Effective as monotherapy in black patients and elderly patients
  - Potentiate ACE inhibitor effects
  - Renal protection not proven
  - Reduce morbidity and mortality rates in congestive heart failure
  - Indicated in patients with diastolic dysfunction
  - No change in dose with renal failure
- Adverse effects
  - Possible increase in cardiovascular mortality rate with short-acting dihydropyridines
  - Edema
  - Constipation (verapamil)
  - Profound bradycardia possible when verapamil and diltiazem used in combination with beta-blocker

Beta-blockers

- Effects and indications
  - Precise mechanism of antihypertensive action unknown
  - Suppress renin secretion
  - Reduce morbidity and mortality rates after myocardial infarction
  - Possible dose adjustment of some beta-blockers required in renal failure
  - Monotherapy less effective in black patients
- Adverse effects
  - Bradyarrhythmia
  - Hypoglycemia unawareness
  - Bronchospasm
  - May precipitate heart failure

- Depression
- Lowers high-density lipoprotein levels and increases triglyceride levels

Vasodilators

- Effects and indications
  - Arteriolar dilation by blocking arterial wall calcium uptake
  - Effective in severe hypertension (minoxidil is better than hydralazine)
  - Minoxidil most potent vasodilator available for oral use
  - No dose adjustment in renal failure
  - Best used in combination with a diuretic plus a beta-blocker
- Adverse effects
  - Reflex activation of sympathetic nervous system (headache, tachycardia)
  - Activation of renin-angiotensin system (sodium retention)
  - Loop diuretic possibly required to control edema
  - Hirsutism (minoxidil)
  - T-wave inversion in approximately 50% of patients on minoxidil

Angiotensin II receptor antagonists

- Effects and indications
  - Reduce proteinuria
  - Indicated in patients intolerant of ACE inhibitors
  - Can be used in combination with an ACE inhibitor
  - Do not cause cough
  - Reduce left-ventricular hypertrophy and thirst similarly to ACE inhibitors
  - Do not interfere with breakdown of bradykinin
- Adverse effects

- Hyperkalemia
- May reduce GFR in patients with impaired renal function
- May precipitate acute renal failure in patient with renal artery stenosis
- Angioedema (rare)
- Data in black patients limited

Central-acting alpha-2 agonists

- Effects and indications
  - Methyldopa drug of choice in pregnancy
  - Hypertensive emergency (clonidine)
  - Clonidine useful when patient has migraine in association with hypertension
- Adverse effects
  - Sedation
  - Orthostatic hypotension
  - Dry mouth, skin irritation (clonidine patch)
  - Rebound hypertension upon abrupt discontinuation
  - Possible Coombs-positive hemolytic anemia with methyldopa

Alpha-1 antagonists

- Effects and indications
  - Improve insulin sensitivity
  - Improve urine flow in patients with benign prostatic hypertrophy
  - Reduce total cholesterol and triglyceride levels and increase high-density lipoprotei
- Adverse effects
  - Orthostatic hypotension
  - Caution when using in patients with autonomic neuropathy

Antihypertensives

Several antihypertensive medications, including thiazide diuretics, beta-blockers, ACE inhibitor and calcium channel blockers, in principle, can be used as initial monotherapy in patients with hypertension. The Joint National Committee on Detection, Evaluation, and Treatment of High I Pressure VII (JNC VII) has recommended the following for uncomplicated hypertension:

- Therapy begins with lifestyle modification.
- If the BP goal is not achieved, thiazide-type diuretics should be used as initial therapy for patients, either alone or in combination with one of the other classes (ie, ACE inhibitors, beta-blockers, calcium channel blockers) that have also been shown to reduce one or m hypertensive complications in randomized controlled outcome trials.
- Selection of one of these other agents as initial therapy is recommended when a diuretic used or when a compelling indication requires the use of a specific drug.
- More than two thirds of hypertensive individuals do not achieve adequate control on one require 2 or more antihypertensive agents selected from different drug classes.
- The initiation of therapy with more than one drug increases the likelihood of achieving th faster. The use of multidrug combinations often produces greater BP reduction at lower c the component agents, resulting in fewer adverse effects.
- Hypertension may exist in association with other conditions with compelling indications f particular treatment based on clinical trial data demonstrating benefits of such therapy or natural history of the associated condition. Compelling indications for specific therapy inv risk conditions that can be direct sequelae of hypertension (eg, HF, ischemic heart disea kidney disease, recurrent stroke) or commonly associated with hypertension (eg, diabete coronary disease risk). Therapeutic decisions in such individuals should be directed at b compelling indication and lowering of BP.

Low-dose thiazides

Low-dose thiazides are now recognized as achieving maximal effects on BP with minimal adv effects. Results from multiple treatment trials show the benefits of low-dose diuretics and alph in preventing stroke, coronary events, congestive heart failure, and all-cause mortality.

ACE inhibitors

With the exception of ACE inhibitors in patients with diabetes, no data indicate the best way to patients with essential hypertension while preserving renal function. However, results obtainec use of different antihypertensive treatment in patients with chronic renal failure and/or diabetes

animal and human studies) may be extrapolated to guide the treatment of patients with essent hypertension.

In animal models of chronic renal failure and diabetes, control of hypertension with the use of inhibitors has been clearly demonstrated, and angiotensin II receptor antagonists can decreas proteinuria, reduce the severity of glomerulosclerosis and interstitial fibrosis, and slow the proc renal disease.

Human studies show that ACE inhibitors are capable of slowing the progression of renal failur forms of nephropathy, except in patients with polycystic kidneys. Based on these and other re inhibitors have become the recommended initial therapy to treat hypertension in patients with

This recommendation is also supported by the results of the Heart Outcomes Prevention Eval (HOPE) trial. According to this study, an ACE inhibitor administered once daily reduces cardio events in patients without heart failure but with at least one cardiovascular risk factor, not inclu diabetes. Similarly, the Microalbuminuria, Cardiovascular, and Renal Outcomes (MICRO-HOP substudy of the HOPE trial randomized 3577 subjects with diabetes who had a prior cardiovas or at least one other cardiovascular risk factor and no clinical proteinuria to receive either rami mg/d) or placebo. Treatment with ramipril resulted in a 24% risk reduction of overt nephropath development after 4.5 years of follow-up care (independent of BP reduction).

The beneficial effect of ACE inhibitors is attributed, at least in part, to their ability to reduce or proteinuria. This is particularly important for patients with diabetes because the development c microalbuminuria is associated with an increased prevalence of cardiovascular complications. studies have suggested that microalbuminuria is an early marker of renal damage in patients v hypertension, and patients with microalbuminuria experience a faster decline in renal function. al (1994) reported a faster decline in creatinine clearance in patients who are hypertensive wit microalbuminuria compared with patients who are hypertensive with normal albumin excretion mL/min vs 2 mL/min). Similar findings were observed by Bianchi et al (1999). In a few studies, inhibitors, but not calcium channel blockers, reduced microalbuminuria in patients with essenti hypertension. Other studies have also confirmed the ability of ACE inhibitors to reduce protein these patients.

Whether a reduction in microalbuminuria results in a decreased prevalence of ESRD in patien hypertension remains to be determined. While combining an ACE inhibitor with a calcium char blocker has been shown to reduce cardiovascular events in clinical trials of hypertension, the renoprotective effects are less uniformly demonstrated. Recent studies, including the Fosinopr Amlodipine Cardiac Events Trial (FACET), the HOT study, and the Systolic Hypertension in Eu (Syst-Eur) trial, have reported conflicting results in terms of both cardiovascular and renal outc

In the FACET, combination therapy with ACE inhibitors and calcium channel blockers resulted significantly lower BPs compared with other groups. Moreover, combination therapy also show best results in reducing the mortality rate. To date, in patients with established renal failure (ie, creatinine >1.4 mg/dL), none of the dihydropyridine calcium channel blockers available in the States has been shown to slow renal disease progression in the absence of an ACE inhibitor.

Alpha-blocker and ACE inhibitor combination

Alpha-adrenergic receptor blockers at low doses may be used as monotherapy in the treatmer

hypertension. Alpha-adrenergic receptor blockers improve insulin sensitivity, improve urine flo total cholesterol and triglyceride levels, and increase high-density lipoprotein levels.

Combinations of alpha-blockers and ACE inhibitors have additive effects for lowering BP only i with a baseline pulse rate that is greater than 84 beats per minute. In terms of slowing renal di progression in patients with diabetes or impaired renal function, alpha-blockers are of no addit benefit. Some patients may require an additional arteriolar vasodilator to control BP. Finally, a II receptor blockers, alone or in combination with other antihypertensive medications, offer a th alternative. Angiotensin II receptor blockers have a favorable adverse effect profile and appea the same beneficial effects of ACE inhibitors; however, no conclusive human data on renal dis progression are available for these agents.

Remember that only approximately 50% of patients with hypertension reach target BP control antihypertensive monotherapy. Approximately 80-90% of patients require a second agent. The of the patients require a combination of 3 or more agents in order to reach target BP control.

Drug Category: *Diuretics* -- Induce natriuresis, reduce target organ morbidity and mortality patients with hypertension, achieve maximal BP-lowering effects at low doses (12.5-25 mg/d), potentiate antihypertensive effects of other BP medications. Antihypertensive effect of these a observed in all demographic groups. Thiazides induce vasodilation and are superior to loop di antihypertensive agents.

Drug Name	Hydrochlorothiazide (Esidrix, HydroDIURIL) -- Inhibits reabsorption of sodium in distal tubules, causing increased excretion of sodium, water, potassium, and hydrogen ions.
Adult Dose	12.5-25 mg/d PO
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; anuria; renal decompensation
Interactions	May decrease effects of anticoagulants, antigout agents, and sulfonylureas; may increase toxicity of allopurinol, anesthetics, antineoplastics, calcium salts, loop diuretics, lithium, diazoxide, digitalis, amphotericin B, and nondepolarizing muscle relaxants
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in renal or hepatic disease, gout, diabetes mellitus, and erythematosus

Drug Category: *Angiotensin-converting enzyme inhibitors* -- Reduce proteinuria, have renal protective effects in both diabetic and nondiabetic renal impairment, and reduce morbidit mortality rates in congestive heart failure. Less effective as monotherapy if patient >50 y. Blac require increased doses. Inhibit or blunt all adverse metabolic effects of thiazides, and reduce ventricular hypertrophy.

Drug Name	Fosinopril (Monopril) -- Prevents conversion of angiotensin I to angiotensin II, a potent

	vasoconstrictor, resulting in lower aldosterone secretion.
Adult Dose	10 mg/d PO initially; may increase to 20-40 mg/d PO
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; history of angioedema
Interactions	NSAIDs may reduce hypotensive effects; may increase digoxin, lithium, and allopurinol levels; rifampin decreases levels; probenecid may increase levels; hypotensive effects may be enhanced when administered concurrently with diuretics
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Category D in second and third trimester of pregnancy; caution in renal impairment, valvular stenosis, or severe CHF
Drug Name	Ramipril (Altace) -- Prevents conversion of angiotensin I to angiotensin II, a potent vasoconstrictor, resulting in lower aldosterone secretion.
Adult Dose	10 mg PO qd
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; history of angioedema
Interactions	NSAIDs may reduce hypotensive effects; may increase digoxin, lithium, and allopurinol levels; rifampin decreases levels; probenecid may increase levels; hypotensive effects may be enhanced when administered concurrently with diuretics
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Category D in first trimester of pregnancy; caution in renal impairment, valvular stenosis, or severe CHF

Drug Category: *Angiotensin II receptor antagonists* -- Indicated in patients intolerant of A inhibitors because they do not interfere with the breakdown of bradykinin or cause cough. Red ventricular hypertrophy and thirst similarly to ACE inhibitors and reduce proteinuria.

Drug Name	Losartan (Cozaar) -- Blocks vasoconstrictor and aldosterone-secreting effects of angiotensin II. May induce a more complete inhibition of renin-angiotensin system than ACE inhibitors, does not affect response to bradykinin, and is less likely to be associated with cough and angioedema. For patients unable to tolerate ACE inhibitors. Angiotensin II receptor blockers reduce BP and proteinuria, protecting renal function and delaying onset of ESRD.

Adult Dose	50 mg PO qd initially; not to exceed 100 mg/d
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity
Interactions	Ketoconazole, sulfaphenazole, and phenobarbital may decrease effects; cimetidine may increase effects
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Caution in patients with unilateral or bilateral renal artery stenosis
Drug Name	Valsartan (Diovan) -- Prodrug that produces direct antagonism of angiotensin II receptors. Displaces angiotensin II from AT1 receptor and may lower BP by antagonizing AT1-induced vasoconstriction, aldosterone release, catecholamine release, arginine vasopressin release, water intake, and hypertrophic responses. May induce more complete inhibition of renin-angiotensin system than ACE inhibitors, does not affect response to bradykinin, and is less likely to be associated with cough and angioedema. For patients unable to tolerate ACE inhibitors.
Adult Dose	80 mg/d PO qd; may increase to maximum 320 mg/d
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; severe hepatic insufficiency; biliary cirrhosis or obstruction; primary hyperaldosteronism; bilateral renal artery stenosis
Interactions	Ketoconazole, troleandomycin, sulfaphenazole, and phenobarbital may decrease effects; cimetidine and monoxidine may increase effects
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in hyperkalemia, suspected bilateral renal artery stenosis, or solitary kidney with unilateral renal artery stenosis

Drug Category: *Calcium channel blockers* -- Effective as monotherapy in black patients a patients. Potentiate ACE inhibitor effects. Renal protection is not proven, but reduce morbidity mortality rates in congestive heart failure. Indicated in patients with diastolic dysfunction.

Drug Name	Verapamil (Calan, Covera, Verelan) -- During depolarization, inhibits calcium ion from entering slow channels or voltage-sensitive areas of vascular smooth muscle and myocardium.
Adult Dose	240-480 mg/d PO divided tid/qid
Pediatric Dose	Not established
	Documented hypersensitivity; severe CHF; sick sinus

Contraindications	syndrome or second- or third-degree AV block; hypotension (<90 mm Hg systolic)
Interactions	May increase carbamazepine, digoxin, and cyclosporine levels; coadministration with amiodarone can cause bradycardia and a decrease in cardiac output; may increase cardiac depression when administered concurrently with beta-blockers; cimetidine may increase levels; may increase theophylline levels
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Hepatocellular injury may occur; transient elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have occurred (elevations have been transient and may disappear with continued treatment); periodically monitor liver function; may cause constipation
Drug Name	Amlodipine (Norvasc) -- Relaxes coronary smooth muscle and produces coronary vasodilation, which, in turn, improves myocardial oxygen delivery. Benefits nonpregnant patients with systolic dysfunction, hypertension, or arrhythmias. Can be used during pregnancy if clinically indicated.
Adult Dose	2.5-5 mg PO qd; not to exceed 10 mg/d
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; severe CHF; sick sinus syndrome; second- or third-degree AV block; hypotension (<90 mm Hg systolic)
Interactions	May increase carbamazepine, digoxin, cyclosporine, and theophylline levels; coadministration with amiodarone may cause bradycardia and decrease in cardiac output; may increase cardiac depression when administered with beta-blockers
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Adjust dose in renal or hepatic impairment; may cause lower extremity edema; allergic hepatitis has occurred but is rare
Drug Name	Felodipine (Plendil) -- Relaxes coronary smooth muscle and produces coronary vasodilation, which, in turn, improves myocardial oxygen delivery.
Adult Dose	5 mg PO qd; not to exceed 20 mg/d
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; severe CHF; sick sinus syndrome; second- or third-degree AV block;

	hypotension (<90 mm Hg systolic)
Interactions	Bioavailability may be decreased with coadministration of barbiturates, carbamazepine, or hydantoins; effects may be increased with coadministration of erythromycin; may increase digoxin and cyclosporine levels; coadministration with amiodarone may cause bradycardia and decrease in cardiac output; may increase cardiac depression when administered with beta-blockers; with coadministration, theophylline levels may be slightly decreased
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Monitor BP closely during dosage adjustment; may cause greater hypotensive effect in elderly patients; adjust dose in renal or hepatic impairment; may cause lower extremity edema

Drug Category: *Beta-adrenergic blocking agents* -- Suppress renin secretion. Monotherа effective in black patients. Reduce morbidity and mortality rates after myocardial infarction.

Drug Name	Labetalol (Normodyne, Trandate) -- Blocks beta1-, alpha-, and beta2-adrenergic receptor sites, decreasing BP.
Adult Dose	100 mg PO bid initially; not to exceed 2400 mg/d
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; cardiogenic shock; pulmonary edema; bradycardia; AV block; uncompensated congestive heart failure; reactive airway disease
Interactions	Decreases effect of diuretics and increases toxicity of methotrexate, lithium, and salicylates; may diminish reflex tachycardia resulting from nitroglycerin use without interfering with hypotensive effects; cimetidine may increase blood levels; glutethimide may decrease effects by inducing microsomal enzymes
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in impaired hepatic function; discontinue therapy if signs of liver dysfunction are present; in elderly patients, a lower response rate and higher incidence of toxicity may be observed

Drug Category: *Vasodilators* -- Cause arteriolar dilation by blocking arterial wall calcium uр Effective in severe hypertension (minoxidil more effective than hydralazine). Best if used in coı with a diuretic plus a beta-blocker.

	Minoxidil (Loniten) -- Most potent vasodilator

Drug Name	available for oral use. Relaxes arteriolar smooth muscle, causing vasodilation, which, in turn, may reduce BP.
Adult Dose	2.5-5 mg PO qd initially; increase gradually to maximum 100 mg/d
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; pheochromocytoma
Interactions	Concurrent use with guanethidine, diuretics, or hypotensive agents may result in additive hypotension
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	May exacerbate angina pectoris; caution in pulmonary hypertension, CHF, coronary artery disease, and significant renal failure
Drug Name	Hydralazine (Apresoline) -- Decreases systemic resistance through direct vasodilation of arterioles.
Adult Dose	10 mg PO qid; not to exceed 300 mg/d
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; mitral valve rheumatic heart disease
Interactions	MAOIs and beta-blockers may increase toxicity; indomethacin may decrease pharmacologic effects
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Implicated in MI; caution in suspected coronary artery disease

Drug Category: *Alpha-adrenergic agonists* -- Improve hemodynamic status by increasing myocardial contractility and heart rate, resulting in increased cardiac output. Also increase per resistance by causing vasoconstriction. Increased cardiac output and increased peripheral res lead to increased BP.

Drug Name	Methyldopa (Aldomet) -- DOC in pregnancy. Mechanism of action is likely due to drug's metabolism to alpha-methyl norepinephrine, which lowers arterial pressure by stimulating central inhibitory alpha-adrenergic receptors, false neurotransmission, or reducing plasma renin activity.
Adult Dose	250 mg PO bid/tid; increase q2d prn; not to exceed 3 g/d
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; active hepatic disease; coadministration with MAOIs
	Coadministration with nonselective beta-blockers

Interactions	may cause paradoxical hypertension; may potentiate antipsychotic effects of haloperidol or produce psychosis; effects of lowering BP with methyldopa may be potentiated by levodopa; central effects of levodopa in Parkinson disease may be potentiated by methyldopa; may need reduced doses of anesthetics; coadministration with lithium may cause lithium toxicity; concurrent use with MAOIs leads to excessive sympathetic stimulation; coadministration with phenothiazines may cause serious BP elevation; may potentiate pressor effects of sympathomimetics; tolbutamide metabolism may be impaired, resulting in enhanced hypoglycemic effects; barbiturates and TCAs may reduce effects
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Perform periodic LFTs (particularly during first 6-12 wk); notify physician of unexplained prolonged tiredness, fever, or jaundice; urine may darken when exposed to air after voiding
Drug Name	Clonidine (Catapres) -- Stimulates alpha-2 adrenoreceptors in brain stem, activating an inhibitory neuron, which results in reduced sympathetic outflow. Decreases vasomotor tone and heart rates. Used in hypertensive emergency. Useful when patient has a migraine in association with hypertension.
Adult Dose	Initial: 0.1 mg PO bid Maintenance: 0.2-1.2 mg/d PO in 2-4 divided doses; not to exceed 2.4 mg/d
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity
Interactions	TCAs inhibit hypotensive effects; coadministration with beta-blockers may potentiate bradycardia; TCAs may enhance hypertensive response associated with abrupt clonidine withdrawal; hypotensive effects enhanced by narcotic analgesics
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in cerebrovascular disease, coronary insufficiency, sinus node dysfunction, and renal impairment
Drug Name	Doxazosin (Cardura) -- Inhibits postsynaptic alpha-adrenergic receptors, resulting in vasodilation of veins and arterioles and decrease in total peripheral resistance and BP.
Adult Dose	1 mg PO hs; not to exceed 16 mg/d

Pediatric Dose	Not established
Contraindications	Documented hypersensitivity
Interactions	Effects decrease with coadministration of NSAIDs; effects increase with coadministration of diuretics and antihypertensive medications
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Caution in renal impairment; may cause marked hypotension following first dose; may worsen CHF

Deterrence/Prevention:

- Hypertension complicating primary renal disease
  - Systemic hypertension clearly induces or accelerates the progression of renal dise experimental models. In these models, BP control reduces proteinuria and prevent deterioration of renal function.
  - Similarly, in a variety of primary human renal diseases, BP strongly predicts a faste the GFR.
  - As demonstrated by the MDRD study, even small differences in mean arterial pres between the usual BP control group and the low-BP group had significant effects ir renal disease progression.

Complications:

- Traditionally, nephrosclerosis was considered the consequence of long-term hypertensic premise is based on observations of rapidly progressive renal failure developing in some with malignant hypertension. Such individuals demonstrate arterial and necrotizing lesior kidneys, which may be reversed with effective BP control. However, less severe hyperte se, is suggested to cause renal failure only rarely, and progressive renal impairment is u secondary to undiagnosed primary renal disease.
  - Madhavan et al (1995) followed the cases of 2125 men with mild-to-moderate hype for 5 years and found no change in serum creatinine values. Similarly, Tomson et a followed the cases of 176 patients with essential hypertension for more than 14 ye found no change in serum creatinine values, with none of the patients developing r failure.
  - In the Baltimore Longitudinal Study on Aging, the cases of 446 patients who are predominantly white and of middle or upper socioeconomic status were followed o year period. In this study, patients with hypertension had a decline in their GFRs at rate than normotensive subjects (0.92 mL/min/y vs 0.75 mL/min/y). Although this st showed that patients with hypertension lost renal function at a faster rate with agin

normotensive subjects, the rate of decline in renal function was small and unlikely t ESRD. More importantly, this study failed to determine whether the decline in renal was secondary to essential hypertension or was the result of undiagnosed primary disease.

- In a review of the British Health System data on hypertension and nephrosclerosis, and Lip (1996) noted that baseline proteinuria or renal impairment was evident at p in all patients who later developed significant renal failure. More importantly, these not find any reported cases of patients who went on to develop renal failure who ha essential hypertension with reference range serum creatinine levels and no eviden proteinuria.

- On the other hand, Rosansky et al (1990) reported on the cases of 56 patients with hypertension, all of whom had creatinine levels within the reference range and no p at the beginning of the observation, and compared them with 59 normotensive con patients. At an average of 9.8 years, the rate of decline in renal function was signifi higher in the patients with hypertension than in the control patients; however, the a stated that the diagnostic criteria for hypertensive renal disease often was not fulfill

- Finally, Klag et al (1996), in the largest prospective trial to date, primarily intended t the cardiovascular risk associated with hypertension. The MRFIT analyzed the cas 332,544 men (90.4% white) whose cases were followed for an average of 16 years study showed a strong graded relationship between BP (the relative risk of develop varied from 2.8-12.4 as diastolic BP increased from 90-120 mm Hg) and the subse development of ESRD; however, most patients with progressive renal failure had a other than essential hypertension. Furthermore, this tendency to develop an elevat serum creatinine level appears to have been largely a feature of the black populati no changes in the reciprocal creatinine slope was observed in white patients; howe significant decline in renal function were observed in the black patients.

- In 1997, the same group of authors (Brancati et al) reevaluated data from the MRF time aiming to determine the relative risk of ESRD related to diabetes. Their conclu that diabetes mellitus is a strong independent risk factor for ESRD, even for ESRD to causes other than diabetes (by year 15 of follow-up, the cumulative ESRD incide had risen to 2.97% in diabetic men). However, if baseline diabetes mellitus is remo risk attributable to hypertension to cause ESRD is almost negligible (0.19%; this nu be actually lower because 8.4% of cases of ESRD in men without diabetes at base classified as diabetic ESRD). Noted that a greater proportion of diabetic men, comp nondiabetic men, were black (12.6% vs 6%). Diabetic men were also approximatel older on average and had higher blood systolic and diastolic pressures than their n counterparts.

- The significant decline in renal function observed in black patients confirmed simila observations by the HDFP. In this study, of the 8000 patients with normal renal fun outset, only 110 had a significant increase in serum creatinine values over time; the was largely confined to black people. In further agreement with Beevers and Lip's (observations outlined above, the patients with the highest serum creatinine levels a presentation had the largest reduction in renal function, implying that subclinical re damage was present from the beginning. Neither the HDFP nor the MRFIT provide

information regarding whether participants had proteinuria at presentation. In additi studies do not rule out the possibility that patients who progressed had some form glomerulonephritis because participants did not undergo renal biopsies.

- Zucchelli and Zuccalà (1993) reviewed the cases of 136 patients who were original diagnosed with benign nephrosclerosis but actually represented a heterogeneous g these patients, a thorough diagnostic workup, including renal biopsy, reconfirmed nephrosclerosis as the correct diagnosis in many of the patients (44%), although 5(patients were reclassified as having cholesterol microembolism (29%) or renovasc hypertension (26.5%). Schlessinger et al (1994) made a similar observation when t reviewed the cases of 233 patients undergoing evaluation as candidates for renal transplantation. Schlessinger et al found that their referring physicians diagnosed 4 patients with ESRD secondary to HN. After extensive review of the patients' medic laboratory evaluations, and available renal biopsy results, the authors concluded th the 43 patients met the clinical criteria for HN.

- A further complication is that many patients already have advanced renal failure at presentation. Qualheim et al (1991) reported that at the time patients with presume presented to a nephrologist, their serum creatinine values were close to 7 mg/dL in patients and 9.4 mg/dL in black patients. Diagnosing HN in these patients can be d impossible because of the inability to identify the initial process. However, in black closer correlation between clinical and histological diagnoses of HN has been repo

- In the AASK, 88 black patients who did not have diabetes or hypertension but who to-moderate renal insufficiency and absent marked proteinuria were asked to unde biopsy. Forty-six patients agreed, and 39 biopsies were performed. The mean arte pressure of these patients was 109 mm Hg ± 15 mm Hg, and their mean GFR was ± 13 mL/min. In nearly 85% of the cases, renal biopsy results showed arteriosclero arteriolosclerosis, interstitial fibrosis, thickening of the basement membrane, and gl glomerulosclerosis consistent with the clinical diagnosis of HN. The conclusion of t was that in black people who do not have diabetes or hypertension but who have d renal function and mild proteinuria, renal biopsy findings are likely to be consistent clinical diagnosis of HN.

- Considering that approximately 60 million individuals with hypertension live in the United only 19,000 (1 in 2200) develop ESRD, factors other than hypertension have been postu participate in the progression of renal failure. Hyperlipidemia, insulin resistance, hyperuri immune-mediated factors, and other unrecognized mechanisms may play a role. In this is possibly a disease primarily of the small renal vessels, with glomerular changes being to the vascular process. Autopsy studies of patients with mild, moderate, and severe vas disease found an independent correlation between glomerulosclerosis and atheroscleros and Appel (1999) found that 52% of white patients diagnosed with HN had at least one f atherosclerosis at baseline.

- Clinical and experimental evidence indicates that histologic lesions indistinguishable fron in conditions associated with BP values within the reference range, such as in patients w syndrome. Nephrosclerosis is also observed spontaneously with aging, especially in pati than 60 years. Diabetes mellitus markedly increases the presence and severity of nephr in all age groups; as such, nephrosclerosis appears to be the common final pathway of s

processes that cause injury to small intrarenal vessels.

Prognosis:

- With regard to the target BP, the Working Group Report on Hypertension and Diabetes r recommended a BP goal of less than 130/80 mm Hg in order to preserve renal function a cardiovascular events in patients with hypertension and diabetes. Lower BPs are recomr patients with proteinuria greater than 1 g/d and renal insufficiency, regardless of etiology optimal BP goal to slow the progression of renal failure in patients with HN currently is ur
- HN remains a poorly defined entity. Researchers continue to search for a clear definition pathophysiologic mechanism, and optimal treatment for patients with this condition. As s by Meyrier (1996), HN may conceivably be a primary microvascular nephropathy.
- Uncontrolled hypertension can accelerate the decline of renal function in patients with pr disease; however, whether mild-to-moderate essential hypertension can cause ESRD in people is uncertain. The available data do not support the hypothesis that high BP is the determining ESRD in these patients.
- Medical treatment is indicated in any patient with BP higher than 140/90 mm Hg. In these antihypertensive treatment has proven to reduce the risk of stroke and cardiovascular m Evidence for the beneficial effect of hypertension treatment on patients with HN is lackin many questions regarding the ability of these drugs to protect renal function in the long te unanswered.

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Medical/Legal Pitfalls:

- Failure to diagnose a treatable cause of hypertension and progressive renal failure by lal patient as having HN without excluding other likely causes

Special Concerns:

- Oral contraceptives (eg, birth control pill) are the most common cause of drug-induced hypertension.

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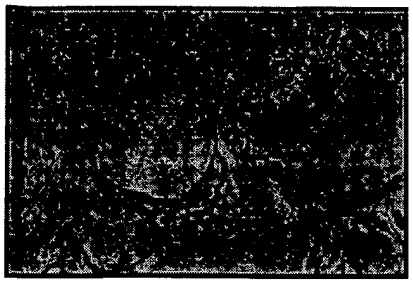
Caption: Picture 1. Nephrosclerosis. The glomerular tuft is shrunken, with wrinkling of the capillary walls (asterisk), global glomerular sclerosis (arrow), and complete obliteration of the capillary loops and glomerular ischemia (periodic acid-Schiff stain at 250X magnification).



View Full Size Image

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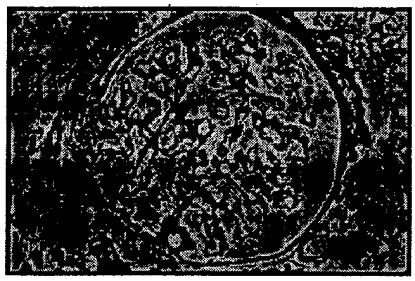
Picture Type: Photo

Caption: Picture 2. Nephrosclerosis. Glomerulus with wrinkling of glomerular basement membranes accompanied by reduction of capillary lumen diameter (silver stain at 400X magnification).



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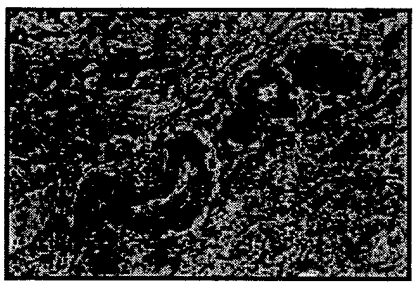
Picture Type: Photo

Caption: Picture 3. Nephrosclerosis. Hyaline arteriosclerosis with hyaline deposits (arrows) (trichrome stain at 250X magnification).



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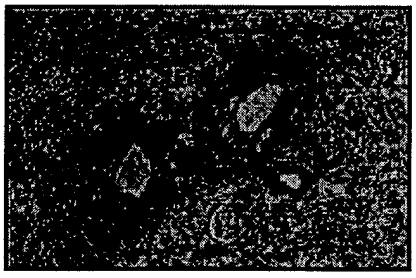
Picture Type: Photo

Caption: Picture 4. Nephrosclerosis. Fibrointimal proliferation of the arcuate artery (periodic acid-Schiff stain at 150X magnification).



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Picture Type: Photo

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EXHIBIT 2

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Nephrology Dialysis Transplantation

Original Article

Renal vascular changes in renal disease independent of hypertension

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Abstract

Introduction. Cardiovascular disease is common in patients with renal disease, but little is known about the effect of renal disease and loss of renal function on vascular morphology. Intima proliferation of small renal arteries, which correlates with atherosclerosis in the aorta, is sometimes present in renal disease and has been shown to increase with age and hypertension. We studied the effect of chronic renal disease and renal function, independent of hypertension, on intima proliferation.

Methods. We retrospectively selected renal biopsies of subjects in whom a glomerular filtration rate (GFR) measurement with [^{125}I] iothalamate had been performed. To separate the effects of renal disease and renal function, we selected biopsies from (A) normotensive controls undergoing nephrectomy because of renal carcinomas; (B) normotensive patients with renal disease and GFR > 90 ml/min; (C) normotensive patients with GFR 30–90 ml/min, and (D) hypertensive patients with a GFR < 90 ml/min. The area of the arteriolar lumen, intima, and media were measured.

Results. No significant changes from control subjects were observed in group B. Intima proliferation was observed when renal function declined (intima/total vessel surface ratio was 0.262 ± 0.071 in group C, 0.192 ± 0.032 in group A, and 0.205 ± 0.035 in group B, $P < 0.05$). The intima proliferation was aggravated in patients with renal insufficiency and hypertension (0.333 ± 0.121, $P < 0.05$). Media surface area was not different between groups.

Conclusion. Renal disease with preserved GFR does not cause significant intima proliferation of small renal arteries. Loss of renal function is accompanied by intima proliferation, even in the absence of systemic hypertension.

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Introduction

Cardiovascular disease is very common in patients with end stage renal disease. Accelerated arterial stiffening and a high prevalence of atherosclerotic lesions contribute to high cardiovascular mortality rates in this population [1–5]. Although relatively little is known about the nature of the vascular changes in earlier stages of renal disease, there appears to be an association with several distinct pathological conditions. Intima proliferation of small renal arteries increases with age [6], and correlates with the extent of atherosclerosis in the aorta and coronary arteries [7]. Intima proliferation of small intrarenal arteries occurs at an accelerated rate in subjects with hypertension and in smokers [6,8]. It has also been observed in patients with renal disease, particularly in patients with IgA nephropathy, with or without hypertension [9–11]. Hypertension is generally considered to play an important role in the pathogenesis of intrarenal vascular changes in patients with renal disease.

The aim of the present study was to separate the effects of renal disease, renal function, and hypertension on vascular pathology of small renal arteries. We therefore compared the renal microvasculature in renal biopsies taken from selected patient groups. Selection was based on the presence of chronic renal disease, on glomerular filtration rate, and on the presence or absence of hypertension.

Subjects and methods

Subjects

We retrospectively analysed renal tissue of patients in whom both a renal biopsy and a [^{125}I] iothalamate glomerular

filtration rate (GFR) measurement had been performed between 1985 and 1999. Subjects with acute renal failure or any type of vasculitis were excluded. Age, diagnosis, GFR, blood pressure level, antihypertensive medication, smoking habits and, if available, total cholesterol levels at the time of the renal biopsy were collected from the patient files.

Four groups were selected:

(A) Normotensive patients in whom nephrectomy was performed, in most cases because of a renal cell carcinoma. In those subjects, no GFR measurement was available.
(B) Patients with chronic renal disease, having a GFR >90 ml/min, without hypertension, (blood pressure <160/90 mmHg, without the use of antihypertensive medication).
(C) Patients with chronic renal disease, without hypertension and a GFR between 30 and 90 ml/min.
(D) Patients with chronic renal disease, and a GFR <90 ml/min, in the presence of hypertension (blood pressure ⩾160/90 mmHg, and/or the use of one or more antihypertensive medications).

Processing of biopsies and morphometry

Paraffin-embedded renal biopsies of all patients included in the study (two tissue samples per patient, groups B, C, D) and tissue blocks containing normal renal parenchyma (group A) were retrieved from the files of the Department of Pathology, Academic Medical Center (AMC). Three-micrometre sections were cut and stained with elastic van Gieson (EvG) and haematoxylin and eosin (H&E) respectively.

For morphometrical analysis, cross-sectional areas of the entire artery (total surface), lumen, intima and media were planometrically quantified in EvG-stained sections using TIM image analysis software on a PC provided with a VS-100-AT frame grabber (Data Measuring Systems, Breda, the Netherlands). Sections were projected on a video screen and the inner border of the intima, the internal elastic lamina (IEL), and the outer border of the vessel (media) were outlined manually. The cross-sectional area of the intima was represented by the surface area enclosed within the inner border of the intima and the IEL. The cross-sectional area of the media was defined as the area enclosed within the IEL and the outer border of the media. All areas were measured automatically, expressed in μm^2, and stored on disk. All arterioles and small arteries in the range from 5000 to 20 000 μm^2 were included in the study. Of these vessels the wall/lumen, lumen/total surface, wall/total surface, intima/total surface, and media/total surface ratios were calculated.

Statistical analysis

Results are expressed as means ± SD. Paired *t*-tests were used to compare results of the different groups, if a one-way ANOVA had shown significant differences to be present. *P* values <0.05 were considered significant. Linear regression analysis was performed to calculate correlation coefficients.

Results

Basic characteristics for all four groups are given in Table 1. All subjects of group A underwent unilateral nephrectomy because of renal cell carcinoma. In group B, five subjects suffered from IgA nephropathy, three from membranous glomerulopathy, one from minimal-change glomerulopathy, and one from focal glomerulosclerosis. In group C, chronic interstitial nephritis was diagnosed in nine patients, and IgA nephropathy and minimal-change glomerulopathy in one patient each. In group D, hypertensive nephropathy was diagnosed in three subjects, IgA nephropathy in two, and mesangioproliferative glomerulopathy and membranous glomerulopathy in one patient each. In group A, no GFR measurements were available. However all subjects in this group had normal serum creatinine values.

Serum cholesterol levels were available in 17 subjects. Serum cholesterol ranged from 5.7 to 10.3 mmol/l ($n=8$) in group B, from 3.9 to 8.7 mmol/l in group C ($n=5$), and from 4.7 to 7.9 mmol/l in group D ($n=4$), with no significant differences between groups.

Histologically the intima thickening consisted of an accumulation of extracellular matrix, including thickening and multiplication of elastin lamellae, in which sparse spindle shaped cells (smooth-muscle cells) were present. There were no obvious structural differences in composition among the four groups, although the formation of concentric lamellae of elastin was most pronounced in the patients with hypertension. Representative examples are shown in Figure 1.

Table 1. Basic characteristics

Group	A Normotensive controls	B GFR >90, normotensive	C GFR 30–90, normotensive	D GFR 30–90, hypertensive
n	12	10	11	7
Age (years)	51 ± 14	36 ± 9	39 ± 15	43 ± 19
Male/female	9 : 3	8 : 2	7 : 4	4 : 3
GFR (ml/min)	NA	118 ± 10	50 ± 11§	48 ± 12 §
Blood pressure (mmHg)				
Systolic	127 ± 12	133 ± 13	128 ± 16	145 ± 21
Diastolic	79 ± 9	81 ± 8	79 ± 11	92 ± 16
Smokers (*n*)	3	4	4	5

*$P<0.05$ *vs* group A, §*vs* group B. NA, not assessed.

The total surface of the vessels studied tended to be largest in group A; the intima surface was largest in group D (Table 2). The wall-to-lumen ratio did not differ between groups A and B. The wall-to-lumen ratio was elevated both in normotensive and hypertensive patients with renal function loss (groups C and D, Table 2). The contribution of the wall area to the total surface area was clearly increased in group C and D.

This increase could be attributed to an increase of intima surface at the expense of luminal surface (Figures 2, 3). The relative media surface was not different among the four groups (Table 2).

We found no significant correlations between age, blood pressure level, serum cholesterol levels, or smoking behaviour, and intima proliferation.

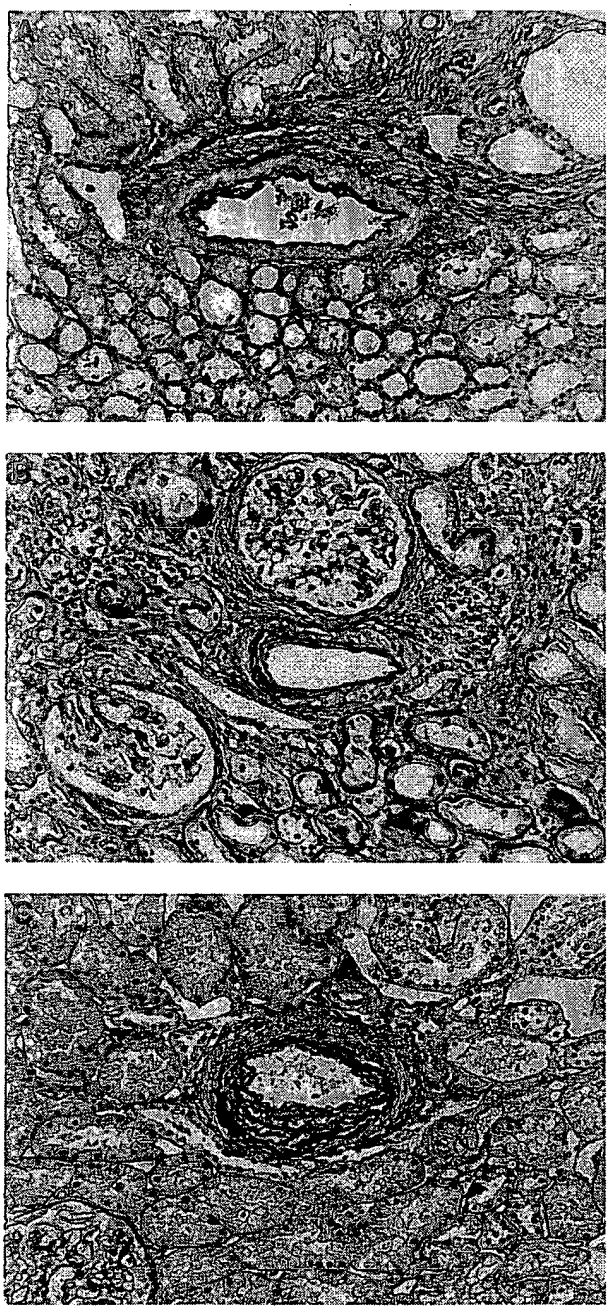

Fig. 1. Histological samples. Representative examples of the light microscopy of small renal arteries in biopsies of patients enrolled in group A (A), group C (B) and group D (C). Elastic van Gieson stain, 175×.

Discussion

In this study we show that renal function loss is accompanied by intima proliferation of renal arterioles, even in the absence of hypertension. This intima proliferation is accelerated in the presence of hypertension. We further show that the mere presence of a renal disease does not cause intima proliferation.

Although we had data of a limited number of patients only, we were able to separate the effects of renal disease, renal function loss, and hypertension. Using [^{125}I] iothalamate GFR measurements, which are more precise in estimating renal function than creatinine clearance, we separated subjects with preserved renal function from those with chronic renal function loss. Since many patients with chronic renal function loss are hypertensive, it has been difficult to separate the effects of renal function loss and hypertension on intima proliferation. Selection of normotensive and hypertensive patients groups allowed us to make this distinction.

We did not observe a significant difference in intima proliferation of small renal arteries between normotensive controls (group A) and normotensive subjects with a renal disease and preserved renal function (group B). However, the age of the control group tended to be higher and the average size of the studied arteries tended to be larger in the control group. Both age [6] and artery size [12] were found to correlate positively with the extent of intima proliferation. Therefore, a small effect of the mere presence of renal disease cannot be completely excluded.

The results in group C show that chronic renal function loss is accompanied by intima proliferation of small renal arteries, even in the absence of systemic hypertension. This increased intima proliferation could not be explained by differences in age, smoking pattern, or cholesterol level. However, other factors have been shown to be involved in the pathogenesis of cardiovascular disease in renal failure. Lipid profiles become more atherogenic and oxidative stress increases, as do cytokine levels and levels of various growth-promoting substances such as angiotensin 2, endothelin, platelet-derived growth factor, and vascular endothelial growth factor [13–16]. The latter substances especially may be involved in smooth-muscle proliferation, which is often present in the expanding intima of renal arteries [11]. The increased arteriolar wall thickening in the absence of hypertension is also in agreement with studies in uraemic animals. In several studies progression, as well as treatment-induced regression, of hypertrophy of

Table 2. Vascular dimensions

Group	A Normotensive controls	B GFR >90, normotensive	C GFR 30–90, normotensive	D GFR 30–90, hypertensive
Arteries in biopsy (n)	2.55±0.93	1.90±0.99	2.09±0.70	2.14±0.90
Total surface (μm^2)	14 086±2 438	10 730±3 684	10 206±4 670	11 344±2 319
Wall/lumen ratio	2.18±0.45	2.76±0.85	3.59±1.51*	5.53±3.45*
Lumen/total surface (%)	32.1±4.6	27.8±5.9	23.9±7.4*	18.8±8.7*§
Wall/total surface (%)	67.9±4.6	72.2±5.9	76.0±7.4*	81.2±8.7*§
Intima/total surface (%)	19.2±3.2	20.5±3.5	26.2±7.1*§	33.3±12.1*§
Media/total surface (%)	48.8±5.5	51.7±7.2	49.9±4.0	47.9±9.1

*$P<0.05$ *vs* group A, § *vs* group B, in t-test.

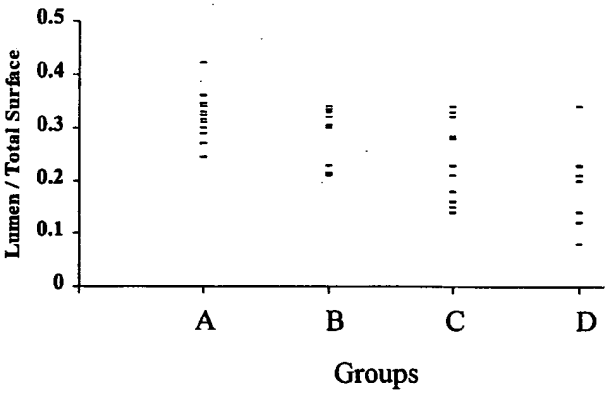

Fig. 2. Luminal surface. Individual luminal surface area normalized for the total surface area (lumen area/total surface area) in percentage. Group A, normotensive controls ($n=12$); group B, normotensive renal patients with GFR >90 ml/min ($n=10$); group C, normotensive renal patients with GFR 30–90 ml/min ($n=11$); group D, hypertensive renal patients with GFR 30–90 ml/min ($n=7$).

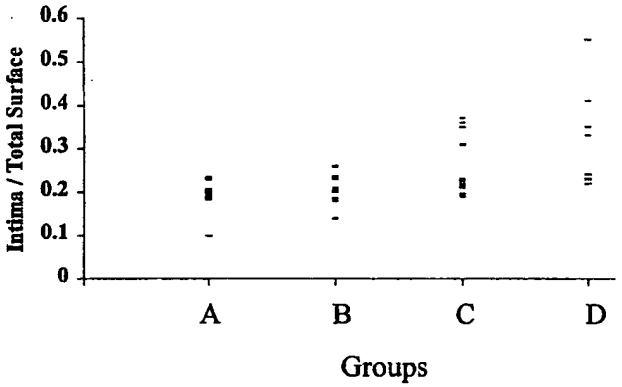

Fig. 3. Intima surface. Individual intima surface area normalized for the total surface area (intima area/total surface area) in percentage. Group A, normotensive controls ($n=12$); group B, normotensive renal patients with GFR >90 ml/min ($n=10$); group C, normotensive renal patients with GFR 30–90 ml/min ($n=11$); group D, hypertensive renal patients with GFR 30–90 ml/min ($n=7$).

cardiac arterioles was shown to be, at least in part, independent of blood pressure [16–18].

Although the increase in intima surface between groups C and D did not reach statistical significance, there seems to be a trend towards increased intima proliferation in hypertensive patients with chronic renal function loss. The use of antihypertensive medication might have affected the intima proliferation in group D. We did not observe an age-dependent increase of the intima surface within the control group, possibly because normotensive subjects were selected. Blood pressure, which increases with age, is more strongly related to intima proliferation than to age [19]. The relatively small sample size of the control group might be another reason why no age-dependent intima proliferation was found.

Media hypertrophy was not found, even in hypertensive subjects. This is in agreement with previous findings in hypertensive rats. Whereas hypertension causes media hypertrophy in other organs, this is not necessarily the case in small renal arteries [20]. Furthermore, arterial remodelling has mainly been shown in arteries that were slightly larger (100–200 μm diameter) [21], than most of the small arteries investigated in the present study. In the hypertensive subjects (group D), the lack of media hypertrophy might be partly explained by the use of antihypertensive agents.

Limitations

The number of normotensive patients in whom both a renal biopsy and a GFR measurement had been performed was limited. Therefore we could not make a distinction between subjects with mild, moderate, and severe renal function loss. However, the main finding of this study, the fact that renal disease with preserved GFR does not cause intima proliferation of small renal arteries, was based on the comparison of the two largest groups, the normotensive controls (group A, $n=12$) *vs* group B normotensive renal patients with GFR >90 ml/min ($n=10$). Testing the significance of the 1.3% difference in intima surface between these groups with a power of 0.8 at a significance level of 0.05 requires a study in which 128 subjects would have to be included in both groups! Although based on

relatively small groups, we think our data provide a strong indication that intima proliferation is not accelerated in normotensive renal patients with a preserved GFR.

The study population is too small to study the effect of individual renal diseases. Furthermore, it cannot be concluded that the increase in intima proliferation observed in group C, the normotensive subjects with decreased GFR, in comparison with group B, the normotensive renal patients with preserved GFR is solely due to the difference in renal function. The fact that group B consisted completely of patients with glomerulopathies, whereas the majority of group C suffered from interstitial nephritis, might have affected our results as well.

We do not think that the use of different sampling techniques (tissue samples obtained after nephrectomy in group A *vs* two transcutaneous renal biopsies in the other groups) introduced a further bias. As detailed in Table 2, the average number of vessels was only marginally larger in group A. We were aware of the risk of studying larger vessels in the groups in which larger tissue specimens were available (group A). By limiting our study to vessels with a total surface area less than 20 000 μm^2, such differences could be prevented.

We conclude that renal disease with preserved GFR does not cause significant intima proliferation of small renal arteries. However, once associated with a loss of renal function, renal disease appears to be accompanied by intimal proliferations, even in the absence of systemic hypertension.

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